REMARKS/ARGUMENTS

Claim 1 has been amended to clarify the meaning of preferential detection of a receptor within a cell. Support is provided at e.g., p. 31, lines 11-14. The amendment should not be construed as acquiescence in the rejection. Claims 1 and 3-77 are pending. Claims 4-13, 17-24, 36, 38, 39, 41-45, 51, 55, 57, 59-65, 67 and 69-77 are withdrawn from consideration.

2. Claims 1, 49, 50, 52, 53, 56, 58, 66 and 68 stand rejected as allegedly anticipated by Boyer. The Examiner states he has not given weight to the claim limitation that the reporter preferentially generates a signal from internalized complexes on the basis that the term preferential can be interpreted to refer to the mind of the investigator. This rejection is respectfully traversed, particularly insofar as it might be applied to the amended claim.

As should be clear from the specification, the description of the reporter preferentially generating a signal from internalized complexes is not referring to the mind of the investigator but rather characterizing a property of the reporter. That is, the reporter, preferentially generates a signal (i.e., generates a greater signal) from internalized complexes relative to complexes bound to the cell surface. Such can be achieved for example, when the reporter is a substrate for an intracellular enzyme (see specification at p. 32), when the reporter is masked (see specification at p. 33), a nucleic acid binding dye, an internally quenched reporter, or a bioactive moiety (see specification at pp. 34-35) among other possibilities. Such a reporter is useful in distinguishing between complexes bound to the cell and complexes internalized within a cell and hence determining which complexes contain a compound that is a substrate for transporters within the cell membrane. By contrast, Boyer used either a fluorescent or radioactive label. There is no reason to think that either label would generate a preferential signal from within the cell; in fact, one would expect the reverse because the cell wall and membrane might partially quench the fluorescent or radioactive signal from within a cell.

For these reasons, Boyer does not anticipate the claims, and it is respectfully submitted the rejection should be withdrawn.

4. All subject matter was commonly owned at all relevant times.

5. Claim 1, 3, 14-16, 25-35, 37, 40, 46-50, 52, 53, 56, 66 and 68 stand rejected as obvious over Boyer in view of Schaeffer and Thompson. This rejection is respectfully traversed.

Schaeffer discusses the use of luciferin linked to a ligand for immunoassays and ligand-receptor assays. Such assays are performed in vitro and do not involve passage of luciferin into cells. Luciferin is mentioned as being advantageous relative to luciferase which has previously been used for such immunoassays due to its relative stability, greater resistance to proteases and smaller size and consequently smaller steric changes. The author concludes that the "successful linkage of luciferin to alpha-BTX suggests that future conjugation of luciferin to *various other ligands* will provide the basis for the development of *sensitive bioluminescent immunoassays and bioluminescent ligand receptor assays*" sentence bridging pp. 2057-20580 (emphasis supplied).

Thompson is directed to methods of gene shuffling materials from several species. In passing, Thompson lists conventional markers for detecting transformation with an expression vector, one of which is the luciferase gene.

"To establish a prima facie case of obviousness based on a combination of the content of various references, there must be some teaching, suggestion or motivation in the prior art to make the *specific* combination that was made by the applicant." *In re Dance,* 160 F.3d 1339, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (emphasis supplied). Motivation must have sufficient "force" to "impel persons skilled in the art to do what applicant has done." *Ex parte Levengood,* 28 USPQ2d 1300, 1302 (BPAI 1993). The motivation must be specific and objective. *In re Dembiczak,* 50 USPQ2d 1614 (Fed. Cir. 1999). The requirement for evidence of particularized motivation provides a safeguard against the "tempting but forbidden zone of hindsight." *Dembiczak* at p. 1616.

Here, none of the motivation alleged by the Office Action would have impelled the artisan to the specific combination claimed. The statement quoted by the Office Action from Schaeffer in the paragraph bridging pp. 2057-2058 refers to development of immunoassays and bioluminescent ligand-receptor assays for other ligands. These are precisely the type of assay described in the rest of the Schaeffer paper. In such an assay, a ligand is used to detect and

quantify an entity to which the ligand binds to a target molecule *in vitro*. Thus, by the quoted statement, Schaeffer is saying no more than that other ligands can be detected using the same type of *in vitro* assay as described in his paper. This does not point to a different type of assay in which luciferin is used not merely to quantify an entity in an *in vitro* sample, but as a means to monitor transport of an entity into a cell.

The statements of Schaeffer quoted by the Office Action regarding its high sensitivity, stability, and lack of sensitivity to proteases are made in the context of comparing luciferin to luciferase as a detection moiety for the immuno and ligand-receptor assays described in the paper (see p. 2057, second column, first paragraph). These statements simply suggest that luciferin is more suitable than luciferase for immuno- and ligand-receptor assays, but provide no indication of other assays in which either luciferin or luciferase might be used.

The only asserted motivation for combining Thompson with Boyer is the passage at col. 12, lines 55-57. This passage states that a major advantage of Thompson's method is that it can be practiced on organisms that do not grow well. This statement does not indicate that Thompson's methods could or should be used to analyze transporters, much less in the manner claimed.

Finally, the Office Action's allegation that one would have reasonably expected success because Schaeffer states that luciferin conjugates can be generally applied to a wide range of systems is incorrect. As discussed above, Schaeffer does not say that luciferin conjugates can be generally applied to a wide range of systems but rather says they can be used for detection of a broad range of ligands in immunoassay or ligand receptor assays. Schaeffer says nothing about using luciferin in other types of assays, particularly the type now being claimed. Likewise, the Office Action's comments regarding Thompson demonstrating the success of luciferin/luciferase reporter systems in high throughput assays is not predictive of the claimed methods. In Thompson's method, DNA encoding luciferase is introduced into a cell in a vector. Such does not suggest or predict the success of introducing luciferin as a molecule linked to a compound, as a means of monitoring passage of the compound into the cell.

For these reasons, it is submitted that no evidence has been provided of any motivation that associates the discussion of luciferin in Schaeffer with anything other than

immunoassays and ligand receptor assays, and that of Thompson with anything other than conventional use of the luciferase gene as a vector marker. In the absence of clear and particular motivation within the teachings of the cited references that would have impelled the artisan toward the specific combination claimed, the combination cannot be said to be obvious.

Many of the dependent claims are distinguished for additional grounds. Claims 25, 27 and 35 specify that the claimed methods are performed on different cells in the same reaction vessels. Against these claims, the Office Action says that the combined references of Schaeffer and Thompson teach different screening formats with different populations of cells. However, the Office Action provided citations only to Thompson, and these citations refer to mixed populations of library cells or mixed populations of library cells and indicator cells. It is not disputed that in some contexts, it is known to mix cells. What is at issue is whether it would have been obvious to do so in the claimed methods. The context of Thompson's mixing cells is entirely different. Thompson mixes cells either in generating or screening expression libraries resulting from gene shuffling. No reason has been provided that the artisan would have seen any connection between whether Thompson does or does not mix cells in the generation and screening of shuffled gene libraries with whether mixtures of cells should be used in screening compounds for capacity to be transported into cells.

Claims 28-34 and 40 are distinguished for similar reasons. The Office Action alleges that the combined references of Schaeffer and Thompson) teach different strains, and epitopes (although the Office Action provides citations only to Thompson). Again, it is not disputed that different strains of cells are known and that strains can be distinguished by different epitopes as markers. What is at issue is whether it would have been obvious to use such different strains in the context of the claimed methods. In the claimed methods, the use of distinguishable strains or markers facilitates simultaneous assays of transport into different cells in the same vessel by allowing the different cells to be distinguished. Thompson uses different strains for an entirely different purpose, namely, to generate diversity in gene shuffling assays. No motivation has been provided as to why the artisan would see any relevance of the use of diverse strains for gene shuffling with the use of different strains to allow multiple transport assays to be conducted simultaneously in the same vessel.

Claim 46 specifies a method containing steps of providing and screening a focused library where the focused library contains variants of a compound shows to be a substrate for a transporter in a previous step. The Office Action alleges that such is suggested by the combined disclosure of Schaeffer and Thompson, but again the Office Action provides citations only to Thompson. Thompson discusses enriching a shuffled DNA library for members having a desired property by screening. Again, it is not apparent how an artisan would see any connection between such teaching and methods employing variants of a compound in assays for a substrate of a transporter.

Claim 48 is directed to isolated a DNA molecule encoding a carrier-type transporter from a cell that has been shown to transport a compound. The Office Action alleges that the combination of Schaeffer and Thompson discloses the isolation of unknown expression products by HTS techniques. Again, the Examiner provides a citation only to Thompson. Thompson merely discloses that "High-throughput screening processes can be used e.g., macrodroplet sorting, fluorescence activated cell sorting or magnetic activated cell sorting, to identify and isolated the desired organisms in a combinatorial gene expression library" (col. 5, lines 60-65). Again, it is not disputed that high throughput processes are known or that genes can be isolated from expression libraries. What is at issue is whether the artisan would have been motivated to, and known how to, modify the teaching of Boyer from a method of identifying a substrate of a known transporter, into a method of identifying a hitherto unknown transporter for a known compound. As the Federal Circuit has cautioned, a "person of ordinary skill is the art is...*presumed to be one who thinks along the lines of conventional wisdom in the art...*," *Standard Oil Co. v American Cyanamid Co.*, 774 F.2d 448 (Fed. Cir. 1985), at p. 454 (emphasis added). Knowledge of standard but general techniques such as expression cloning and high throughput screening is not enough for the artisan to depart from conventional wisdom in the art to achieve the claimed invention.

For all these reasons, it is respectfully submitted the rejection should be withdrawn.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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Attachments

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